REMARKS

Claims 57-60, 63-81, 83-104 are currently pending in the subject application. Claim 84 is withdrawn from consideration by the Examiner under 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Claims 57-60, 63-81, 83 and 85-103 are currently under consideration and stand rejected under 35 U.S.C. §§102, 103 and 112 based on a number of positions laid out in detail in the 8/19/04 Office Action. Applicant respectfully disagrees with the conclusions set forth in that office action. The Amendments presented in this paper are being made solely to expedite prosecution, rather than in acquiescence with any positions taken by the Examiner. In fact, Applicant is *not* acquiescing to any of those positions and is submitting this amendment without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be lost by virtue of this paper. Applicant explicitly reserves the right to pursue this subject matter in divisional or continuation applications.

Applicant has amended claims 57-58, 64, 66-67, 69, has canceled claims 65 and 70, and has added claims 105-107. All the other claims remain unchanged. Below we address each of the rejections stated in the Office Action as if it were applied to the newly amended claims.

Amendments to Claims

Claim 57 has been amended to recite a "biological component" in step c, and to further define the step of assaying for association between the antibody and the biological component. Without conceding the correctness of the Examiner's position with respect to alleged § 112, 1st paragraph issues with respect to steps d)-g), but solely to expedite prosecution, Applicant has deleted these steps from claim 58. Support for the amendments made to claim 58 can be found, for example, in Example 12 pages 97-98, and Figure 13 of the specification as filed. Claims 64, 66 and 67. Claim 69 has been amended to change claim dependency. New claims 105-107 find support, for example, in Example 12 pages 97-98, and Figure 13 of the specification as filed.

No new matter is presented with these amendments.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 58-59, 63, 65, 71-81, 83 and 85-104 under 35 U.S.C. § 112, first paragraph and states that the specification does not sufficiently teach the method of claim 58 comprising steps d) through g).

Applicant strongly disagrees. The specification makes it clear that Applicant was indeed in possession of the invention as claimed in claim 58, as pending prior to the present amendment, at the time the invention was made. As taught throughout the specification and figures, a "functional fingerprint" represents a collection of information on effects of a test compound on a plurality of biological or chemical processes. Applicant points to, for example, lines 7-14 page 42 of the specification:

> *The present invention provides a system whereby chemical compounds can be fingerprinted based on the changes that they induce in a variety of different cellular processes, including, for example, protein concentration, phosphorylation, methylation, acetylation, lipidation, isoprenylation, ubiquitination; second messenger concentration; and the rate or extent of DNA synthesis. The total pattern of these alterations constitutes an effective "fingerprint" (i.e. biological profile) of each bioactive agent. Example 12 describes one embodiment of functional fingerprinting according to the present invention.* Emphasis added.

Applicant submits that the Application, as filed, clearly conveys how the claimed method can be used to gather a collection of information regarding the effects of test compounds on a variety of biological or chemical processes in a high-throughput fashion, and that this collection of information constitutes a "functional fingerprint." Applicant asserts that the skilled artisan wishing to built a "functional fingerprint" for one or more test compounds would know, based on Applicants' teachings, how to use the claimed invention to collect information regarding the effects of test compounds on a variety of biological or chemical processes. The skilled artisan would recognize that this can be accomplished according to various experimental designs. Whether the information constituting the functional fingerprint is collected by using a different antibody in each reaction vessel (e.g., Example 12), a different antibody across a row of reaction vessels and the same antibody down a column of reaction vessels (e.g., Figure 13), a different antibody in each array of reaction vessels (e.g., claim 58, as pending prior to the amendment presented herein), or variations thereof, is irrelevant. Each embodiment of the method would allow the collection of effects on biological or chemical processes for one or more test compounds; *i.e.*, a functional fingerprint, and is well within the scope of the invention. Example 12 and Figure 13 are merely *examples* of how the collection of test compounds' effects may be

gathered to build the functional fingerprint, and are not meant, nor should they be construed, to limit the scope of the invention.

In addition, Applicant points out that steps d)-g) of claim 58, as pending prior to presentation of this amendment, merely reflect repetition of steps a)-c) at least one time. Applicant asserts that they were in possession of steps a)-c) at the time the invention was made (e.g., claim 57). Therefore, Applicant was necessarily in possession of a method comprising repeating steps a)-c) a number of times, whether the steps are repeated with the same or a different antibody.

Nevertheless, without acquiescing to the Examiner's position, but solely in an effort to expedite prosecution, Applicant has deleted steps d)-g) from claim 58. Therefore, the rejection is now moot. However, Applicant reserves the right to pursue the subject matter of claim 58, as pending prior to this amendment, in Continuation Applications.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 57-60, 63-81, 83 and 85-104 under 35 U.S.C. § 112, second paragraph based on a number of positions detailed below:

a) the Examiner states that the term "component" in claims 57 and 58 has insufficient antecedant basis. Claims 57 and 58 now recite "biological component." Therefore, the rejection is now moot.

b) the Examiner alleges that the step of "retaining the information as a functional fingerprint" is vague and indefinite because it is unclear as to which "information" is being retained. The claims, as amended, do not recite the language objected to, therefore the objection is now moot. Applicant asserts that the claims, as amended, particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

c) the Examiner alleges that the step of "retaining the information as a functional fingerprint" is vague and indefinite because it is unclear as to how retaining the assay information would produce a "functional fingerprint." The claims, as amended, do not recite the language objected to, therefore the objection is now moot. Applicant asserts that the claims, as amended, particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

d) the Examiner alleges that claim 73 is vague and indefinite because it is unclear how it further limits claim 72. Applicant respectfully disagrees and submits that claim 72 recites a step of *providing* the one or more solutions, while claim 73 further comprises a step of *contacting* the cells with the one or more solutions. Claim 73 recites a "contacting" step that is different from the step of "providing" in claim 72. Therefore, claim 73 properly further limits claim 72. Applicant respectfully requests that the stated rejection be withdrawn.

e) the Examiner alleges that claims 57 and 58 are incomplete because they lack the correlation step between the association of the antibody and the component with the test compound. Claim 57, as amended, recites "assaying for association between the antibody and the biological component in the reaction vessels to assess the presence or amount of the biological component, thereby revealing the effect of the test compound on the given biological or chemical process." Similarly, claim 58, as amended, recites "assaying for association between the antibody and the biological component in each reaction vessel to assess the presence or amount of the biological component, thereby revealing the effect of the test compound on the given biological or chemical process." Applicant respectfully submits that claims 57 and 58 are now clear, and respectfully requests that the stated rejection be withdrawn.

Rejection under 35 U.S.C. § 102(b)

Claims 57, 69, 71-72 and 88-90 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Lam *et al.* (U.S. Patent No.: 5,510,240). Specifically, the Examiner states that Lam *et al.* disclose a library of bio-oligomers and several methods of determining biological activities of its members. The Examiner further states that the biological activity in cells is determined by a known MTT assay wherein MTT is added to each well of the bioassay plate, and the product of the MTT metabolism is measured for optical density at 570 nm (citing column 25 line 57 through column 26 line 10).

Applicant points out that the colorimetric MTT assay alluded to by the Examiner is based on the conversion of the water-soluble MTT to an insoluble purple formazan. MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) is taken up by living cells, where it is reduced to a blue-black formazan crystal (in the cells mitochondria). The formazan is then solubilized, and its concentration, determined by optical density at 570 nm, is correlated to the number of living cells in the system being assayed. To the best of Applicant's knowledge, the

MTT assay does not involve an antibody that associates intracellularly with a biological component, nor does it involve assaying for association between the antibody and the biological component. In fact, Applicant fails to find *any* description in the sections identified by the Examiner, or anywhere in the Lam *et al.* reference, of a high-throughput assay comprising steps of introducing into each of a plurality of reaction vessels (i) a plurality of cells, (ii) one or more test compounds whose effect on an intracellular biological or chemical process is to be evaluated, and (iii) *an antibody characterized in that it associates intracellularly with a biological component whose presence or amount reveals the effect of a given test compound on the biological or chemical process*; and (iv) *assaying for association between the antibody and the biological component in the reaction vessels to assess the presence or amount of the biological component, thereby revealing the effect of the test compound on the biological or chemical process*; wherein the plurality of reaction vessels comprises at least 96 reaction vessels. If Applicant is mistaken, the Examiner is invited to point out where, in the sections of the Lam *et al.* reference identified in the 8/19/04 Office Action is found any reference to an antibody that associates intracellularly with a biological component or a step of assaying for association between the antibody and the component in the reaction vessels (*e.g.*, wells). Applicant contends that, absent an explicit description of the presently claimed invention in the Lam *et al.* reference (*i.e.*, including ***all*** the claim limitations), the cited reference cannot be held to anticipate the instant claims.

Applicant asserts that the rejection under 35 U.S.C. § 102(b) over the Lam *et al.* reference is improper, and hereby respectfully requests that the stated rejection be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner has levied § 103 rejections over various combinations of cited art, including Stylli *et al.* (U.S. patent 5,985,214), Photiou *et al.* (European Journal of Cancer, 33(3):463-470, March 1997), Walsh *et al.* (U.S. Patent No.: 5,990,092) and Lam *et al.* (U.S. Patent No.: 5,510,240).

Applicant respectfully disagrees with the conclusions of the Examiner, and maintains that the Examiner has failed to establish a *prima facie* case of obviousness because at least one of the legal requirements for establishing a *prima facie* case of obviousness is not met. Specifically, the legal standard for establishing a *prima facie* case of obviousness requires that three basic criteria

be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success in the modification or in the combination; and (3) the prior art reference must teach all the claim limitations. All three requirements must be met to establish a *prima facie* case of obviousness. In addition, the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure (MPEP 706.02(j)).

Applicant will show below that each of the cited combination of references relied upon by the Examiner fails to establish a *prima facie* case of obviousness because at least one the above requirements is not met.

1. Rejection under 35 U.S.C. § 103(a) over Stylli et al. (U.S. patent 5,985,214) and Photiou et al. (European Journal of Cancer, 33(3):463-470, March 1997)

Claims 57, 59-60, 63-71, 76-81, 83 and 85-104 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stylli *et al.* and Photiou *et al.*

The Examiner states that Stylli *et al.* teach an automated method and system for identifying chemicals having useful activity (*e.g.*, biological activity). The Examiner also states that Stylli *et al.* disclose that the method/system may be used with a variety of cell-based assays. However, the Examiner concedes that Stylli *et al.* do not explicitly teach that the method/system may be applied to a cell-based assay involving an antibody that associates intracellularly with a biological component, and a secondary ligand that binds to the antibody.

The Examiner states that Photiou *et al.* teaches an indirect immunofluorescence method in which cells are seeded on glass cóver slips placed in 24-well plates, treated with drug(s), fixed, permeated, incubated with rabit antitubulin antobodies, washed, and incubated with goat anti-rabbit antibody conjugated to FITC (secondary ligand), citing column 1 page 465). The Examiner concedes that Photiou *et al.* do not disclose a method using 96 wells (reaction vessels). In fact, as detailed in previous responses to Office Actions, the Photiou *et al.* reference does not provide *any* teaching or suggestion that the cell-based assays disclosed in the Photiou *et al.* reference can be carried out in high-throughput format (*e.g.*, with 96 or higher reaction vessels), nor does it provide any teaching or suggestion as to how this might be accomplished.

First of all, Applicant submits that since (i) Stylli *et al.* do not explicitly teach that the method/system may be applied to a cell-based assay involving an antibody that associates intracellularly with a biological component and a step of assaying for association between the antibody and the component in the reaction vessels; and (ii) the Photiou *et al.* reference does not provide *any* teaching or suggestion that the cell-based assays disclosed in Photiou can be carried out in high-throughput format; the combination of cited references cannot be held to provide some suggestion or motivation to modify the references or to combine the reference teachings to arrive at Applicant's claimed invention. The conditions for establishing a *prima facie* case of obviousness are clearly not met.

Secondly, Applicant respectfully submits that the Stylli *et al.* reference, in combination with Photiou *et al.*, cannot provide reasonable motivation to one skilled in the art to use the 24-plate cell-based assay of Photiou according to the method of Stylli, *because there is no reasonable expectation of success in the combination.*

As previously discussed in Applicant's recent responses to Office Actions, cell-based assays were notoriously difficult to automate at the time the invention was made. Applicant points to the Final Conference Program of LabAutomation '98 held in San Diego, CA January 17-21, 1998 (hereinafter referred to as "the Final Conference Program of LabAutomation '98 reference"), cited by this Examiner and the Examiner before her, in the 12/18/02 and 09/05/03 Office Actions. That reference supports the position that high-throughout assay formats, such as those taught by Stylli *et al.*, cannot reasonably be expected to be successfully used for *any* cell-based assay known in the art at the time (*e.g.*, cell-based assays disclosed in the Photiou *et al.*reference). The Final Conference Program of LabAutomation '98 reference reports the existence of high-density plates (*e.g.*, 96-, 384-, 1536- and 10,000-well plates), but specifically teaches that "*some cell-based assays remain difficult to automate*" (See page 159 first paragraph). In fact, despite the existence of 96-, 384-, 1536- and 10,000-well plates at the time, as detailed on page 159, Henderson *et al.* were only able to develop a *24-well* system for the cell-based assays in question. Therefore, based on the Final Conference Program of LabAutomation '98 reference, the skilled artisan would conclude that the mere existence of automated high-density assay formats, such as those taught by Stylli *et al.*, does not imply or suggest that they can *successfully* be used for *any* cell-based assay known in the art at the time.

Applicant notes that the "Examples" section in the Stylli *et al.* reference (Columns 48-62) does not provide *any* experimental data demonstrating that the automated system/method can successfully be used in any cell-based assays. The Examples merely recommend the use of a particular reservoir system if cells are to be dispensed (Column 59 lines 20-32), but do not provide *any* support that cell-based assays have been tried, much less that the outcome was successful. Because the Final Conference Program of LabAutomation '98 reference teaches that cell-based assays cannot be conducted in high-throughput formats with any reasobale expectation of success, the suggestion by Stylli *et al.* that their method can be tried with cell-based assays does not mean, nor does it provide reasonable motivation, that it can be done successfully, much less with *any* cell-based assays.

In light of the Final Conference Program of LabAutomation '98 reference, one of ordinary skill in the art could not expect, at the time the invention was made, that the method of Stylli *et al.* could *successfully* be used to conduct the cell-based assay of Photiou *et al.* in high-throughput format, because there is no specific teaching (*i.e.*, experimental data) in either cited reference supporting a reasonable expectation of success. Therefore, even if there were suggestion or teaching in the references cited by the Examiner to combine the teachings of Stylli *et al.* with the teachings of Photiou *et al.*, there would be no reasonable expectation of success in the combination.

In summary, none of the cited references provide any specific teaching or suggestion to modify or combine the teachings of Stylli *et al.* with the teachings of Photiou *et al.* to achieve the claimed invention. In addition, there would be no reasonable expectation of success in the combination. Accordingly, the stated combination of references cannot be held to render obvious the claimed invention. Applicant respectfully requests that the § 103(a) rejection over Stylli and Photiou be withdrawn.

2. Rejection under 35 U.S.C. § 103(a) over Stylli et al. (U.S. patent 5,985,214) and Photiou et al. (European Journal of Cancer, 33(3):463-470, March 1997), in further view of Walh et al. (U.S. patent 5,990,092).

Claims 72-75 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stylli *et al.*, Photiou *et al.* and Walsh *et al.*

The Examiner states that Walsh *et al.* teach a BrdU assay involving adding BrdU to cells in growth media for 24 hours, fixing and permealizing the cells, and identifying proliferating cells with a mouse anti-BrdU antibody coupled to FITC.

Firstly, Applicant notes that the Examiner relies on the combination of the Stylli *et al.* and Photiou *et al.* references as teaching a high-throughout method for screening test compounds involving cell-based assay comprising introducing an antibody that associates with a biological component, and introducing a secondary ligand that binds specifically with the antibody. Applicant asserts that the Examiner's proposition is improper. The combination of Stylli and Photiou does not, and cannot be held to, teach a high-throughout method for screening test compounds involving cell-based assay whereby an antibody associates with a biological component, and a secondary ligand binds to the antibody. In fact, as demonstrated in section 1 above, the cited combination does not even provide reasonable motivation and expectation of success to the skilled artisan to achieve the claimed invention.

Secondly, Applicant respectfully submits that the combination of Stylli, Photiou and Walsh fails to support a *prima facie* case of obviousness for reason detailed in section 1 above. Specifically, none of the Photiou and Walsh references specifically teach or suggest that the cell-based assays that they describe can be performed in high-throughput format (*e.g.*, number of reaction vessels $\geq$ 96), according to the claimed invention. Since Stylli *et al.* do not explicitly teach that the method/system may be applied to a cell-based assay involving an antibody that associates intracellularly with a biological component and a step of assaying for association between the antibody and the component in the reaction vessels; and the Photiou *et al.* and Walsh *et al.* references do not provide *any* teaching or suggestion that the cell-based assays disclosed in these references can be carried out in high-throughput format, the combination of cited references cannot be held to provide some suggestion or motivation to modify the references or to combine the reference teachings to arrive at Applicant's claimed invention.

In addition, Applicant respectfully submits that the Stylli *et al.* reference, in combination with Photiou *et al.* and Walsh *et al.*, cannot provide reasonable motivation to one skilled in the art to use the cell-based assay of Walsh (and/or Photiou for that matter) according to the method of Stylli, *because there is no reasonable expectation of success in the combination.* Specifically, based on the Final Conference Program of LabAutomation '98 reference, one of ordinary skill in the art could not expect, at the time the invention was made, that the method of Stylli *et al.* could

successfully be used to conduct the cell-based assay of Walsh *et al.* (or any other cell-based assays) in high-throughput format. In the Examples, Stylli et al. merely recommend the use of a particular reservoir system if cells are to be dispensed (Column 59 lines 20-32), but do not provide *any* support that cell-based assays have been tried, much less that the outcome was *successful.* As noted above, the Final Conference Program of LabAutomation '98 reference teaches that cell-based assays are difficult to automate. Therefore, one of ordinary skill in the art would not be motivated to use the cell-based assay of Walsh *et al.* (or Photiou *et al.*) according to the method of Stylli *et al.* because there is no specific teaching (*i.e.*, experimental data) in any of the cited references supporting a reasonable expectation of success. Therefore, even if there were suggestion or teaching in the references cited by the Examiner to combine the teachings of Stylli *et al.* with the teachings of Walsh *et al.* and Photiou *et al.*, there would be no reasonable expectation of success in the combination.

Accordingly, the stated combination of references cannot be held to render obvious the claimed invention. Applicant respectfully requests that the § 103(a) rejection over Stylli, Photiou and Walsh be withdrawn.

3. Rejection under 35 U.S.C. § 103(a) Photiou et al. (European Journal of Cancer, 33(3):463-470, March 1997)* and Lam *et al. (U.S. patent 5,510,240).

Claims 57-60, 63-71, 76-81, 83 and 85-104 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Photiou *et al.* and Lam *et al.*

Applicant respectfully submits that the combination of Photiou and Lam fails to support a *prima facie* case of obviousness for reasons detailed in section 1 above. Specifically, the Photiou reference does not specifically teach nor suggest that the 24-plate cell-based assay can be performed in high-throughput format (*e.g.*, number of reaction vessels $\geq$ 96), according to the claimed invention. In addition, Lam *et al.* does not teach or suggest a cell-based assay involving *an antibody characterized in that it associates intracellularly with a biological component*; and *assaying for association between the antibody and the biological component.* As discussed previously, the MTT assay referred to by the Examiner does not involve an antibody that associates intracellularly with a biological component, nor does it involve assaying for association between the antibody and the biological component. Since Lam *et al.* do not

explicitly teach that a high-throughput format may be applied to a cell-based assay involving an antibody that associates intracellularly with a biological component and a step of assaying for association between the antibody and the component in the reaction vessels; and the Photiou *et al.* reference does not provide *any* teaching or suggestion that the 24-plate cell-based assay disclosed therein can be carried out in high-throughput format, the combination of cited references cannot be held to provide some suggestion or motivation to modify the references or to combine the reference teachings to arrive at Applicant's claimed invention.

In addition, Applicant respectfully submits that the Lam *et al.* reference, in combination with Photiou *et al.*, cannot provide reasonable motivation to one skilled in the art to use the cell-based assay of Photiou with the 96-well plates used by Lam *et al.*, *because there is no reasonable expectation of success in the motivation.* Specifically, based on the Final Conference Program of LabAutomation '98 reference, one of ordinary skill in the art could not expect, at the time the invention was made, that 96-well plates used by Lam *et al.* could *successfully* be used to conduct the cell-based assay of Photiou *et al.* (or any other cell-based assays) in high-throughput format. None of the cited references provide specific teaching (*i.e.*, experimental data) supporting the proposition that the cell-based assay of Photiou *et al.* can *successfully* be used in high-throughput format. As noted above, the Final Conference Program of LabAutomation '98 reference teaches that cell-based assays are difficult to automate. Therefore, one of ordinary skill in the art would not be motivated to use the cell-based assay of Photiou *et al.* with the 96-well plates used by Lam *et al.* because there is no specific teaching (*i.e.*, experimental data) in any of the cited references supporting a reasonable expectation of success. Therefore, even if there were suggestion or teaching in the references cited by the Examiner to combine the teachings of Lam *et al.* with the teachings of Photiou *et al.*, there would be no reasonable expectation of success in the combination.

Accordingly, the stated combination of references cannot be held to render obvious the claimed invention. Applicant respectfully requests that the § 103(a) rejection over Lam et al. and Photiou et al. be withdrawn.

In summary, Applicant has clearly demonstrated that the cited combinations of references do not meet the legal standard for establishing a *prima facie* case of obviousness. Specifically, there is no teaching or suggestion in any of the cited references to modify or combine the

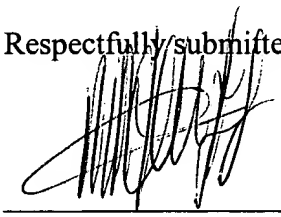
teachings of any of the cited references to achieve the claimed invention. In addition, Applicant has established that there is no reasonable expectation of success in the various cited combinations. Accordingly, the rejections under 35 U.S.C. § 103(a) levied in the 8/19/04 Office Action are improper.

CONCLUSION

Based on the Remarks presented above, Applicant submits that the claims, as amended herein, are allowable over the art of record. The claims are fully supported by the specification and the amendments presented in the present paper do not present new matter. The patent should issue. A Notice to that effect is respectfully requested.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required for consideration of this paper (including fees for net addition of claims) are authorized to be charged to our Deposit Account No. 03-1721.

Respectfully submitted



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